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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,928	CHIAUR ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11,13,14 and 16-36* is/are pending in the application.

4a) Of the above claim(s) *1-6,11 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,13,14,16 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/24/07 has been entered.

[2] Claims 1-7, 11, 13-14, and 16-48 pending in the application.

[3] Applicant's amendment to the claims, filed on 10/24/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's amendment to the specification, filed on 10/24/07, is acknowledged.

[5] Applicant's arguments filed on 10/24/07 in response to the Office action mailed on 4/24/07 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Restriction/Election

[7] Claims 1-6, 11, and 17-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Election was made without traverse in the reply filed on 6/12/2006.

[8] Claims 7, 13-14, 16, 29-48 are being examined on the merits.

Sequence Compliance

[9] Applicant's instant amendment to the specification to incorporate a statement regarding the sequence listing filed on 2/8/07 is acknowledged. However, the instant amendment fails to *direct entry* of the sequence listing into the specification. In order to perfect sequence compliance, applicant should submit an amendment to the specification directing entry of the sequence listing paper copy filed on 2/8/07. Since the instant specification amendment is unnecessary, applicant may consider removing the instantly added text at p. 6, line 28 of the specification.

Claim for Domestic Priority

[10] Applicant's instant amendment to the specification to delete the continuing data at p. 1, lines 3-8 is acknowledged. According to the instant response, "Applicants hereby disclaim priority" to parent application 09/385,219 and provisional applications 60/098,355, 60/118,568, and 60/124,449. As such, the instant application is accorded a priority date of 8/23/03.

[11] If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e) and 120, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the

title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

Claim Rejections - 35 USC § 112, Second Paragraph

[12] Claims 7, 13-14, 16, and 29-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7, 13 (claims 29, 31, 33, and 35 dependent therefrom), 14 (claims 16, 30, 32, 34, and 36 dependent therefrom), 37 (claims 38-42 dependent therefrom), and 43 (claims 44-48 dependent therefrom) are indefinite in the recitation of "βTrcp2" as it is unclear from the specification and the claims as to the scope of polypeptides that are intended as being encompassed by the term "βTrcp2." According to the specification, "βTrcp2" is a polypeptide that belongs to the F-box family of proteins (pp. 1-2 and 5). In construing the meaning of the term "βTrcp2", it is noted that the specification initially sets forth a narrow "definition" of "βTrcp2" (specification at p. 4, line 22 to p. 5, line 26) and then broadly defines these terms as having essentially any structure and any function (specification at p. 40). It is suggested that applicant clarify the meaning of the term "βTrcp2."

RESPONSE TO ARGUMENT: Applicant argues the claims have been amended to require "βTrcp2" to comprise at least one biological activity of endogenous βTrcp2

and that a skilled artisan would recognize the scope of intended polypeptides considered to be a "βTrcp2" when read in light of the specification.

Applicant's argument is not found persuasive. As noted above and in previous Office actions, the specification fails to clearly define those characteristics of a "βTrcp2" polypeptide that distinguish such a polypeptide from other F-box proteins such that a skilled artisan would recognize the intended meaning of the term "βTrcp2". In the absence of such clear definition and in view of the specification's conflicting narrow and broad descriptions of a "βTrcp2" as noted above, it remains unclear as to the intended scope of "βTrcp2" polypeptides.

[13] Claims 7, 13-14, 16, and 29-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 (claims 13, 29, 31, 33, and 35 dependent therefrom), 14 (claims 16, 30, 32, 34, 36 dependent therefrom), 37 (claims 38-42 dependent therefrom), and 43 (claims 44-48 dependent therefrom) are indefinite in the recitation "hybridizes under moderately stringent conditions" (claims 7 and 14) or "hybridizes under highly stringent conditions" (claims 37 and 43) because the specification does not clearly define what conditions constitute "moderately stringent" or "highly stringent". What hybridization conditions are considered "moderately stringent" or "highly stringent" varies widely in the art depending on the individual situation as well as the person making the determination. It is acknowledged the specification states, "highly stringent conditions,

e.g., hybridization to filter-bound DNA in 0.5 M NaHPO4, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65 C, and washing in 0.1xSSC/0.1% SDS at 68 C (Ausubel, et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, atp. 2.10.3)" (p. 30, lines 22-26) and "moderately stringent conditions, e.g., washing in 0.2xSSC/0.1% SDS at 42 C (Ausubel, et al., 1989, supra)" (p. 30, lines 29-31). However, these "definitions", being provided as examples, are considered to be non-limiting. As such it is unclear as the scope of nucleic acids that are intended as being encompassed by parts (ii) of claims 7, 14, 37, and 43. It is suggested that applicant clarify the meanings of the noted phrases.

[14] Claims 7, 13, 29, 31, 33, 35, and 37-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of claims 7 (claims 13, 29, 31, 33, and 35 dependent therefrom) and 37 (claims 38-42 dependent therefrom) recites "A method for screening compounds useful for the treatment of proliferative and differentiative disorders..." However, the two active method steps of the claims, *i.e.,* "contacting..." and "detecting a change...", fail to provide an active step that selects for those compounds that will be "useful" in accordance with the preamble of the claims. In the absence of such a selection step, the claimed methods appear to be incomplete as "screening" for those compounds considered to be "useful" has not been achieved.

Claim Rejections - 35 USC § 112, First Paragraph

[15] Claims 7, 13-14, 16, and 29-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

The claims are drawn to a method using a cell that comprises (in relevant part) a genus of "FBP1" or "βTrcp2" proteins, wherein the "FBP1" or "βTrcp2" protein is recombinantly expressed. Based on the specification's disclosure at p. 40, it appears that the structure of the "FBP1" or "βTrcp2" protein has essentially any structure and biological activity. Although it is acknowledged that the claims recite the structural limitation of the FBP1 protein as being SEQ ID NO:2 or a protein "encoded by a nucleic acid that hybridizes...to the complement of a nucleic acid sequence of SEQ ID NO:1", it is noted that since the phrase "a nucleic acid of SEQ ID NO:1" uses the indefinite article "a", the phrase can be broadly, but reasonably interpreted as a subsequence or

fragment of SEQ ID NO:1 of as few as two contiguous nucleotides of SEQ ID NO:1. Also, it is noted that the phrase "the complement" is not limited to a "full-length" complement. Thus, "a nucleic acid molecule that hybridizes...to the complement of a nucleic acid sequence of SEQ ID NO:1" encompasses essentially any nucleic acid encoding an "FBP1" polypeptide. Also, while claims 7 and 37 functionally limit the genus of FBP1 and βTrcp2 polypeptides to having "at least one biological activity of endogenous FBP1 and βTrcp2, respectively", it is noted that a "biological activity" of a polypeptide can be broadly, but reasonably interpreted as encompassing the ability to elicit an antibody, which "activity" is shared by essentially any polypeptide of sufficient length to serve as an antigen. Claims 14 and 43 functionally limit the genus of FBP1 and βTrcp2 proteins to being "capable of promoting the degradation of IKBα". However, this function encompasses numerous biological activities in various signal transduction pathways that both directly and indirectly "promote" degradation of IKBα. See, *e.g.,* pp. 1-4 of the instant specification.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means

that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of FBP1 polypeptides, *i.e.*, SEQ ID NO:2, and only a single representative species of βTrcp2 polypeptides, *i.e.*, the βTrcp2 polypeptide disclosed by Kipreos and Pagano, *Genome Biol* 1:3002.1 (cited by applicant at p. 5, lines 16-17 of the specification). The specification fails to describe any additional representative species of the recited genus of polypeptides.

While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In the instant case, the recited genus of polypeptides encompasses species that are widely variant in both structure and function. For example, the specification discloses that FBP1 and βTrcp2 are F-box proteins (p. 5, line 25) and the F-box proteins of the invention may be mutants, homologues, or allelic variants (specification at pp. 32-33 and 37), which could have any function or activity, including non-functional proteins. The recitation of "FBP1" or "βTrcp2" fails to provide a sufficient description of the recited genus of proteins as it merely describes the "functional" features of the genus without providing any definition of the structural features of the species within the genus. This functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the protein species within the

genus from other proteins such that one can visualize or recognize the identity of the members of the genus. *Regents of the University of California v. Eli Lilly*, (43 USPQ2d 1398). As such, the disclosure of the single representative species as noted above is insufficient to be representative of the attributes and features of all species encompassed by the recited genus of FBP1 and βTrcp2 polypeptides.

Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

RESPONSE TO ARGUMENT: Applicant argues the rejection is obviated by amendment to recite a structural limitation for the FBP1 protein, *i.e.*, parts (i) and (ii) of claims 7, 14, 37, and 43, and to further recite a functional limitation for FBP1 and βTrcp2 as having "at least one biological activity of endogenous FBP1 and βTrcp2, respectively" (claims 7 and 37) or to being "capable of promoting the degradation of IKBα" (claims 14 and 43). Applicant argues the claimed methods require the use of biologically active FBP1 and βTrcp2 and because the specification discloses a working example of each of a FBP1 and βTrcp2 polypeptide, a skilled artisan can make and test those variants of FBP1 and βTrcp2 encompassed by the claims. According to applicant, in view of these added structural functional limitations in combination with the disclosure of the specification, including assays for determining FBP1 and βTrcp2 activities, the specification adequately describes the genus of FBP1 and βTrcp2 polypeptides.

Applicant's argument is not found persuasive. The examiner acknowledges applicant's amendment to the claims and the cited disclosure of the specification. However, even in view of the instant amendment and noted disclosure, the genus of "FBP1" and "βTrcp2" polypeptides encompasses widely variant species with respect to both structure and function and the single disclosed species of each respective genus fails to reflect the variation among the members of the genus. Although applicant takes the position that one can make and test for additional species other than the single disclosed species of FBP1 and βTrcp2 polypeptides for those that are encompassed by the claims, it is noted that this "make and test" rationale would not appear to be sufficient to satisfy the written description requirement. The Court in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." See also *Ex Parte Kubin* 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007), which states, "Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." In this case, the specification discloses only a single representative species of each respective genus, wherein the single disclosed species are not representative of the entire genus of FBP1 and βTrcp2 polypeptides, particularly in view of the broad "definition" of a FBP1 and βTrcp2 polypeptide in the specification. Thus, at least for the reasons of record and the reasons set forth above, it is the examiner's position that the

specification fails to adequately describe all members of the genus of FBP1 and βTrcp2 polypeptides.

[16] Claims 7, 13-14, 16, and 29-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for screening compounds that are potentially useful for the treatment of proliferative and differentiative disorders by detecting a change in the activity of FBP1 of SEQ ID NO:2 and βTrcp2 as disclosed by Kipreos and Pagano (*supra*) in an isolated cell or extract thereof by monitoring the degradation of IKBα and selecting those compounds that alter the degradation of IKBα as potentially useful for the treatment of proliferative and differentiative disorders, does not reasonably provide enablement for all methods as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

According to MPEP 2164.08, "'the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation'" (emphasis added). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior

art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims...claims are to be given their broadest reasonable interpretation that is consistent with the specification."

The claims are drawn to methods for screening compounds useful for the treatment of proliferative and differentiative disorders. As noted above, the claimed methods use a cell that comprises (in relevant part) a genus of "FBP1" or "βTrcp2" proteins, wherein the "FBP1" or "βTrcp2" protein is recombinantly expressed and wherein the "FBP1" or "βTrcp2" protein has "at least one biological activity of endogenous FBP1 and βTrcp2 protein, respectively. Based on the specification's disclosure at, *e.g.*, pp. 32-33, 37, and 40, it appears the structure of the "FBP1" or "βTrcp2" protein has essentially any structure and biological activity. Although it is acknowledged that the claims recite the structural limitation of the FBP1 protein as

being SEQ ID NO:2 or a protein "encoded by a nucleic acid that hybridizes...to the complement of a nucleic acid sequence of SEQ ID NO:1", it is noted that since the phrase "a nucleic acid of SEQ ID NO:1" uses the indefinite article "a", the phrase can be broadly, but reasonably interpreted as a subsequence or fragment of SEQ ID NO:1 of as few as two contiguous nucleotides of SEQ ID NO:1. Also, it is noted that the phrase "the complement" is not limited to a "full-length" complement. Thus, "a nucleic acid molecule that hybridizes...to the complement of a nucleic acid sequence of SEQ ID NO:1" encompasses essentially any nucleic acid encoding an "FBP1" polypeptide. Also, while claims 7 and 37 functionally limit the FBP1 and βTrcp2 polypeptides to having "at least one biological activity of endogenous FBP1 and βTrcp2, respectively", it is noted that a "biological activity" of a polypeptide can be broadly, but reasonably interpreted as encompassing the ability to elicit an antibody, which "activity" is shared by essentially any polypeptide of sufficient length to serve as an antigen. Claims 14 and 43 functionally limit the FBP1 and βTrcp2 proteins to being "capable of promoting the degradation of IKBα". However, this function encompasses numerous biological activities in various signal transduction pathways that both directly and indirectly "promote" degradation of IKBα. See, *e.g.,* pp. 1-4 of the instant specification. Moreover, in view of the specification's disclosure that "The FBP gene products can also be expressed in transgenic animals" (*e.g.,* pp. 44-45), the "cell" in claims 7, 14, 37, and 43 has been broadly, but reasonably interpreted as encompassing a cell within a transgenic animal, including a human, recombinantly expressing the "FBP gene product" of FBP1 or βTrcp2 as encompassed by the claims.

The enablement provided by the specification is not commensurate in scope with the claimed methods. In this case, the specification is enabling only for methods for screening compounds that are potentially useful for the treatment of proliferative and differentiative disorders by detecting a change in the activity of FBP1 of SEQ ID NO:2 and βTrcp2 as disclosed by Kipreos and Pagano (*supra*) in an isolated cell or extract thereof by monitoring the degradation of IKBα and selecting those compounds that alter the degradation of IKBα as potentially useful for the treatment of proliferative and differentiative disorders.

The amount of direction provided by the inventor and The existence of working examples: The specification discloses only a single working example of an FBP1 or a βTrcp2 polypeptide, *i.e.,* FBP1 of SEQ ID NO:2 and βTrcp2 as disclosed by Kipreos and Pagano (*supra*). The specification fails to disclose any working examples of variants or mutants of SEQ ID NO:2 and βTrcp2 as disclosed by Kipreos and Pagano (*supra*) that maintain the activity of SEQ ID NO:2 or βTrcp2 as disclosed by Kipreos and Pagano (*supra*), respectively. Also, the specification fails to disclose any specific guidance for altering the polypeptide of SEQ ID NO:2 or the βTrcp2 as disclosed by Kipreos and Pagano (*supra*) with an expectation that the resulting variants as encompassed by the claims will maintain the desired activity/utility.

Moreover, it is noted that the use of the claimed invention is in identifying a compound that is "useful for the treatment of proliferative and differentiative disorders" and the specification fails to provide guidance for using those compounds that may modulate the activity of a *variant* of SEQ ID NO:2 and/or the βTrcp2 as disclosed by

Kipreos and Pagano (*supra*), but fail to have a similar effect on SEQ ID NO:2 and βTrcp2 as disclosed by Kipreos and Pagano (*supra*).

Also, the specification provides only a single working example of a transgenic animal, *i.e.,* a transgenic mouse. See Example 12, beginning at p. 116 of the specification. Other than this working example, the specification fails to provide any guidance for making any other transgenic animal, including a human, as encompassed by the claims when interpreted in light of the specification.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: MPEP 2164 states, "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.'" Although it is acknowledged that the claims do not require "a perfected, commercially viable embodiment", the preambles of the claims nonetheless indicate that the screening methods select for those compounds that are *useful* for treatment, suggesting that the compounds are immediately applicable to achieving a therapeutic effect. However, it is noted that while a skilled artisan may recognize that the claimed methods are useful for identifying compounds that are *potentially* useful, the claimed methods would provide no definitive indication as to whether the compounds *are* useful for treating such disorders. This is particularly true of claims 7 and 37, which fail to provide for a step of selecting for those compounds that may be potentially useful for such treatment. In the absence of such a method, one of skill in the art would recognize the high level of unpredictability that the compound would even be *potentially* useful for

achieving a therapeutic effect. Even in claims 14 and 43, which provide for a "mental step" of selecting for those compounds, it is noted that determination of whether or not a compound is "useful" for achieving a therapeutic effect would appear to require more than merely an indication of whether the compound modulates degradation of IKBα. For example, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 9:4227-4239, 2003) acknowledges that "Both basic science studies and clinical trials are essential components of the cancer drug discovery process" (p. 4227, column 2, top).

Regarding the recited FBP1 and βTrcp2 polypeptides, it is noted that the amino acid sequence of a polypeptide determines its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.*, multiple substitutions. At the time of the invention, methods for isolating or generating variants and mutants of a given polypeptide were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the

polypeptide of SEQ ID NO:2 with an expectation of obtaining a polypeptide having the desired activity/utility. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, the reference of Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teaches "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The teachings of Branden et al. are exemplified by the reference of Witkowski et al. (*Biochemistry* 38:11643-11650, 1999; cited in the PTO-892 filed on 8/8/06), which teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647). See also MPEP 2144.08.II.A.4.(c), which states, "[i]n the area of biotechnology, an exemplified species may differ from a claimed species by a conservative substitution ("the replacement in a protein of one amino acid by another, chemically similar, amino acid... [which] is generally expected to lead to either no change or only a small change in the properties of the protein." Dictionary of Biochemistry and Molecular Biology 97 (John Wiley & Sons, 2d ed. 1989)). The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative

substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., Molecular Cell Biology 51 (2d ed. 1990)." "[I]f one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art." See MPEP § 2164.03.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all polypeptides having a substantial number of modifications as encompassed by the claims for those that maintain "the activity" of SEQ ID NO:2 and/or the βTrcp2 as disclosed by Kipreos and Pagano (*supra*).

Also, while methods of producing transgenic animals was known in the art at the time of the invention, it was not routine to produce all transgenic animals as encompassed by the claims, including transgenic humans, for screening compounds as encompassed by the claimed methods.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary

skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: Applicant argues the instant specification coupled with information in the prior art provides considerable direction and guidance on how to make and use the claimed invention, particularly in view of the amendment to recite a structural limitation for the FBP1 protein, *i.e.,* parts (i) and (ii) of claims 7, 14, 37, and 43, and to further recite a functional limitation for FBP1 and βTrcp2 as having "at least one biological activity of endogenous FBP1 and βTrcp2, respectively" (claims 7 and 37) or to being "capable of promoting the degradation of IKBα" (claims 14 and 43). Applicant argues the claimed methods require the use of biologically active FBP1 and βTrcp2 and because the specification discloses a working example of each of a FBP1 and βTrcp2 polypeptide, a skilled artisan can make and test those variants of FBP1 and βTrcp2 encompassed by the claims. According to applicant, in view of these added structural functional limitations in combination with the disclosure of the specification, including assays for determining FBP1 and βTrcp2 activities, the specification enables the full scope of the claimed invention without requiring undue experimentation.

Applicant's argument is not found persuasive. The examiner acknowledges applicant's amendment to the claims. The examiner further acknowledges that the analysis of the enablement requirement under 35 U.S.C. 112, first paragraph, is made in view of the disclosure of the specification in combination with the state of the art at the time of the invention. However, even in view of the instant amendment, the specification's disclosure, and the state of the art at the time of the invention, the examiner maintains the position that the full scope of the claimed invention is not enabled without requiring undue experimentation. See the above detailed analysis of the Factors of *In re Wands* as set forth above. In this case, it is the examiner's position that the specification is enabling only for methods for screening compounds that are potentially useful for the treatment of proliferative and differentiative disorders by detecting a change in the activity of FBP1 of SEQ ID NO:2 and βTrcp2 as disclosed by Kipreos and Pagano (*supra*) in an isolated cell or extract thereof by monitoring the degradation of IKBα and selecting those compounds that alter the degradation of IKBα as potentially useful for the treatment of proliferative and differentiative disorders.

Claim Rejections - 35 USC § 102

[17] Claim(s) 7, 13-14, 16, and 29-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Yaron et al. (*EMBO J* 16:6486-6494, 1997; cited in the PTO-892 filed on 8/8/06; "Yaron-1"). The claims are drawn to screening assays comprising steps of contacting a compound with a cell or extract thereof comprising FBP1, βTrcp2, and IKBα, wherein FBP1, βTrcp2, or IKBα is recombinantly expressed, and detecting a

change in a FBP1 or βTrcp2 activity, or determining the ability of the compound to modulate the degradation of IKBα.

The reference of Yaron-1 teaches a method for assaying degradation of phosphorylated IKBα protein in a reticulocyte extract in the presence and absence of ATP and in the presence of ATP and various peptides by measuring levels of IKBα protein by Western blotting (paragraph bridging pp. 6488-6489 and p. 6489, Figure 4). Under the disclosed assay conditions, the level of phosphorylated IKBα is decreased in the presence of ATP or ATP and peptides ppFos or p21 as compared to the level of phosphorylated IKBα in the absence of ATP (compare Lanes 1 and 2 of Figure 4). Also, the level of phosphorylated IKBα is increased in the presence of peptides pp21 and pp19 as compared to the level of phosphorylated IKBα in the absence of peptides pp21 and pp19 (compare Lane 2 with Lanes 3 and 4 of Figure 4). Yaron-1 further teaches assaying the level of ubiquitinated phosphorylated IKBα in the presence of peptide pp19 (p. 6488, top and p. 6489, Figure 3B, compare Lanes 1 and 6) and also assaying the level of ubiquitinated phosphorylated IKBα in the presence of peptide pp21 and reticulocyte lysate fraction II (p. 6490, Figure 5A, compare Lanes 1 and 4), which resulted in an increase in ubiquitinated phosphorylated IKBα as compared to no peptide. This anticipates claims 7, 13-14, 16, and 29-48 as written.

The following comments are provided to clarify the instant rejection. While Yaron-1 may not characterize the disclosed methods as being screening assays "for screening compounds useful for the treatment of proliferative and differentiative disorders" and may not disclose teachings regarding FBP1 and/or βTrcp2 or interaction thereof with

IKBα, it is noted that, in order for the reference to anticipate the claimed invention, it would appear that the reference need not *expressly* disclose such teachings. The reference need only *expressly or inherently* teach the active method steps as set forth in the method claims. The cell of Yaron-1 inherently expresses FBP1, βTrcp2, and IKBα, and inherently detects a change in FBP1 or βTrcp2 activity by measuring degradation of and/or phosphorylation of IKBα, which is undisputed by applicant. See particularly MPEP 2112.II, which states, "[t]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference." Similarly, it would appear that the Yaron-1 reference is not required to teach the intended use of the compounds identified in the screening methods, namely for treatment of proliferative and differentiative disorders, particularly in view of MPEP 2111.02.II, which states, "[i]f the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." In this case, the claims require only that the cell or cell extract comprise FBP1, βTrcp2, and IKBα, one of FBP1, βTrcp2, and IKBα is recombinantly expressed and detecting a change in the activity of FBP1 or βTrcp2, including degradation of IKBα, in the presence of a test compound.

While Yaron-1 does not appear to *expressly* teach detecting a change in the activity of FBP1 or βTrcp2, including degradation of IKBα, it is noted that applicant states in the response filed on 2/8/07 at p. 14, middle:

> "The instant specification teaches that E3 ubiquitin ligases, which are key enzymes involved in the ubiquitin-mediated proteolysis of proteins are comprised of three subunits: Cdc53, Skp1 and an F-box protein (FBP) and that the interaction of the E3 ubiquitin ligases with target substrates (proteins targeted for degradation) occurs via the FBP (see, e.g., the specification at p. 87, l. 27 to p. 88, l. 5). The instant specification further teaches that FBP1 and βTrcp2 are FBPs that have substrate specificity for IKBα and promote IKBα degradation (see, e.g., the specification at p. 4, ll. 22 to p. 5, ll. 26; p. 87, l. 27 to p. 88, l. 5). Thus, when FBP activity is inhibited, degradation of IKBα will be inhibited and higher levels of IKBα protein will be detected as compared to a cell with normal FBP activity. Likewise, if FBP activity is enhanced, degradation of IKBα will be enhanced and lower levels of IKBα protein will be detected as compared to a cell with normal FBP activity. The instant specification teaches that FBP1 and βTrcp2 activity can be determined by different methods, for example, detecting binding between FBP 1 and IKBα or βTrcp2 and IKBα, by detecting ubiquitination of IKBα, or by detecting a change in the protein levels of IKBα (see, e.g., the specification at p. 9, l. 31 to p. 10, l. 8; p. 91, 1. 20 to p. 92, l. 3; p. 70, ll. 22 to 28)."

Thus, according to applicant, a change in the activity of FBP1 or βTrcp2 can be detected by detecting ubiquitination of IKBα and measuring a change in the protein levels of IKBα. In this case, the reference of Yaron-1 teaches a method for assaying degradation of phosphorylated IKBα protein in the presence and absence of ATP and in the presence of ATP and various peptides by measuring levels of IKBα protein by Western blotting (paragraph bridging pp. 6488-6489 and p. 6489, Figure 4). According to the results of Yaron-1, the level of phosphorylated IKBα is decreased in the presence of ATP or ATP and peptides ppFos or p21 as compared to the level of phosphorylated IKBα in the absence of ATP (compare Lanes 1 and 2 of Figure 4) and the level of phosphorylated IKBα is increased in the presence of peptides pp21 and pp19 as compared to the level of phosphorylated IKBα in the absence of peptides pp21 and pp19 (compare Lane 2 with Lanes 3 and 4 of Figure 4). Yaron-1 further teaches

assaying the level of ubiquitinated phosphorylated IKBα in the presence of peptide pp19 (p. 6488, top and p. 6489, Figure 3B, compare Lanes 1 and 6) and also assaying the level of ubiquitinated phosphorylated IKBα in the presence of peptide pp21 and reticulocyte lysate fraction II (p. 6490, Figure 5A, compare Lanes 1 and 4), which resulted in an increase in ubiquitinated phosphorylated IKBα as compared to no peptide. As such, even though the reference of Yaron-1 is silent regarding FBP1 or βTrcp2, the assays of Yaron-1, by measuring levels of IKBα by Western blotting or by measuring levels of ubiquitinated IKBα, would nonetheless appear to necessarily detect a change in the activity of FBP1 or βTrcp2.

Also, although Yaron-1 does not appear to *expressly* teach FBP1, βTrcp2, or IKBα is "recombinantly expressed" as required by the claims, it is noted that this limitation would nonetheless appear to be satisfied by the teachings of the Yaron-1 reference for at least two reasons. First, it is noted that the recited limitation "the βTrcp2, IKBα, or FBP1 is recombinantly expressed" would appear to be a "product-by-process" type limitation and that such a "product-by-process" would not appear to distinguish over the prior art. As noted in *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989), "[w]hile the present claims are drafted in the form of a compound or a composition, the rationale underlying appellants' arguments is founded on the proposition that the claims are directed to a product-by-process. In any event, we are convinced that the legal philosophy employed in rejections involving products-by-process should be employed with respect to the claims before us. That is, insofar as we can observe, the difference between the material of Goldstein and of Walker and that

claimed by appellants herein resides in the method of obtaining the human growth factor. The prior art material is recovered from natural sources and purified, while appellants' is produced by recombinant DNA methodology. However, the dispositive issue before us is whether the claimed factor exhibits any unexpected properties compared with that described by the cited publication items."

As in *Ex parte Gray,* the difference between the method of Yaron-1 and the claimed method appears to be that the FBP1, βTrcp2, or IKBα is endogenous to the cell extract, while the recited FBP1, βTrcp2, or IKBα is "recombinantly produced". However, that the FBP1, βTrcp2, or IKBα is "recombinantly produced" would not appear to distinguish the recited method from that of the prior art. In this case, applicant presents no evidence of unobviousness between the FBP1, βTrcp2, or IKBα of the lysate of Yaron-1 and that of the claimed method and it is unclear as to how a "recombinantly expressed" FBP1, βTrcp2, or IKBα as encompassed by the claims is different from the FBP1, βTrcp2, or IKBα of Yaron-1.

According to MPEP 2113, "'[i]f the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)... Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Secondly, the "wherein the βTrcp2, IKBα, or FBP1 is recombinantly expressed" limitation would appear to be taught by Yaron-1 since essentially any protein that is expressed in a eukaryotic cell would be broadly, but reasonably considered to be "recombinantly expressed" by virtue of the excision of the intron sequence and recombining of the exon sequence during processing of RNA to form mRNA that occurs during transcription.

Also, while Yaron-1 is silent with regard to the sequence of FBP1 in the cell extract, it is noted that this limitation would also appear to be satisfied by the reference of Yaron-1 for reasons that follow. The FBP1 is defined (in relevant part) in the claims as being encoded by a nucleic acid that hybridizes under moderately or highly stringent conditions to the complement of a nucleic acid of SEQ ID NO:1. Since the phrase "a nucleic acid of SEQ ID NO:1" uses the indefinite article "a", the phrase can be broadly, but reasonably interpreted as a subsequence or fragment of SEQ ID NO:1 of as few as two contiguous nucleotides of SEQ ID NO:1. Thus, "a nucleic acid molecule that hybridizes...to the complement of a nucleic acid sequence of SEQ ID NO:1" encompasses essentially any nucleic acid encoding an "FBP1" polypeptide. As such, the FBP1 of the extract of Yaron-1 would satisfy the noted limitation.

Further, it is noted that Yaron-1 is silent as to the limitation of "wherein a change in degradation of IKBα in the presence of the compound relative to the absence of the compound identifies the compound as a compound useful for the treatment of proliferation and differentiative disorders" in claims 14 and 43. This limitation does not appear to be an active method step and instead is taken to be a "mental step" and as an

intended use of active method step (b). According to MPEP 2111.04, "Claim scope is not limited by claim language that suggests or makes optional but does not require steps to be performed...", including "statements of intended use" (see MPEP 2106.II.C). In this case, the "wherein a change in degradation...identifies the compound..." limitation, being a "mental step" and an "intended use" limitation, does not require active steps to be performed and as such does not appear to limit the claimed methods such that the methods are distinguished over the reference of Yaron-1.

[18] Claim(s) 7, 13-14, 16, and 29-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Yaron et al. (*Nature* 396:590-594, 1998; cited in the PTO-892 filed on 8/8/06; "Yaron-2"). The claims are drawn to screening methods as described above.

The reference of Yaron-2 teaches a method for assaying the level of ubiquitination of phosphorylated IKBα protein or the level of phosphorylated IKBα protein in a HeLa cell pre-incubated with TNF-α, which satisfies parts (a) of claims 7, 14, 37, and 43, followed by incubation of an immunoprecipitated IKBα/NF-KB complex in the presence or absence of a pp10 peptide, and detecting the level of IKBα polypeptide, which satisfies parts (b) of claims 7, 14, 37, and 43. Yaron-2 teaches the presence of TNF-α decreased the level of ubiquitinated phosphorylated IKBα protein as compared to no TNF-α (p. 591, Figure 1, compare lanes 2 and 3). Yaron-2 further teaches a method for assaying the level of ubiquitination of phosphorylated IKBα protein or the level of phosphorylated IKBα protein in the presence or absence of IKK by transforming a HeLa cell with a vector encoding IKK, where the presence of IKK increased the level of

phosphorylated ubiquitinated IKBα protein as compared to no IKK treatment (p. 591, Figure 2a, compare lanes 1 and 3). This anticipates claims 7, 13-14, 16, and 29-48 as written.

See the above discussion regarding clarification of the rejection with respect to the Yaron-1 reference, which is reiterated herein. This discussion equally applies to the Yaron-2 reference.

RESPONSE TO ARGUMENT: Beginning at p. 17 of the instant response, applicant argues the claimed methods are distinguished over the Yaron-1 and -2 references because the references fail to teach or suggest: 1) "that FBP1 and βTrcp2 are involved in the degradation of IKBα" and 2) the cells and extracts of Yaron-1 and -2 do not expressly or inherently express a recombinant FBP1, βTrcp2, or IKBα. Regarding argument 1), according to MPEP 2112.II, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference...'[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.'" As such, the references need not teach the involvement of FBP1 and βTrcp2 in the degradation of IKBα to anticipate the claimed invention.

Regarding argument 2), for at least the two reasons set forth above, the limitation requiring FBP1, βTrcp2, or IKBα be "recombinantly expressed" does not distinguish the claimed methods over the prior art.

Conclusion

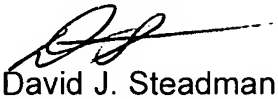
[19] Status of the claims:

- Claims 1-7, 11, 13-14, and 16-36 are pending.
- Claims 1-6, 11, and 17-28 are withdrawn from consideration.
- Claims 7, 13-14, 16, and 29-36 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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